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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,906	05/26/2006	Kohji Fukatsu	20039.0005USWO	7379
52835 7590 02/18/2010 HAMRE, SCHUMANN, MUELLER & LARSON, P.C. P.O. BOX 2902 MINNEAPOLIS, MN 55402-0902			EXAMINER KATAKAM, SUDHAKAR	
			ART UNIT 1621	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/580,906	Applicant(s) FUKATSU ET AL.	
	Examiner SUDHAKAR KATAKAM	Art Unit 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 December 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 7-9, 12-14 and 19-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 10, 11, 15-18 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/24/06, 10/10/06, 2/28/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Restriction

1. Applicant's election of group I (claims 1-18 and 26) in the reply filed on 7 Dec 2010 is acknowledged.

Applicants further elected a species (example 161), and it reads the claims 1-6, 10, 11, 15-18 and 26.

Claims 7-9, 12-14 and 19-25 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 7 Dec 2009.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 3 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound of formula (I) or an agent, which regulates stress, or salt, does not reasonably provide enablement for "acceptable prodrug of a compound of formula (I) or an agent" as claimed. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a

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disclosure does not satisfy the enablement requirement and whether any necessary experimentation undue”.

In *In re Wands*, 8 USPQ2d 1400; CAFC, 1988, factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112 first paragraph, have need described. They are:

1. The nature of the invention,
2. The state of the prior art,
3. The predictability or lack thereof in the art,
4. The amount of direction or guidance present,
5. The presence or absence of working examples,
6. The breadth of the claims,
7. The quantity of experimentation needed, and
8. The level of the skill in the art.

(1). **Nature of the invention:** The claimed invention is drawn to a compound of formula

(I) or an agent, which regulates stress, or its salts or a prodrug.

(2). **Breadth of the claims:** The claims are extremely broad.

Pharmaceutically acceptable prodrugs, the breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) or an agent which regulates stress, as well as the presently unknown list of potential prodrug derivatives embraced by claims 3 and 16-18.

(3). **State of the Prior Art:**

Pharmaceutically acceptable prodrugs, Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low

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expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

(4). Unpredictability of the Art:

With reference to pharmaceutically acceptable prodrugs, it is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(5). Amount of Guidance Provided:

Pharmaceutically acceptable prodrugs, applicants define the "prodrug" in general in the specification. However, there is no further information or guidance provided regarding how one of skilled person in the art would effectively use applicants' disclosure.

(6). Presence or Absence of Working Examples:

There are no working examples of "prodrug" of a compound of formula (I) or an agent, which regulates the stress, in the specification.

(7). Ordinary Skill in the Art: The ordinary skill in the art is high.

(8). Amount of Experimentation Necessary:

In light of the state of art, the unpredictability of the art and amount of guidance provided, as discussed above, the amount of experimentation necessary to practice the current methods is undue. While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various prodrug moieties, reaction conditions, temperature, starting materials without any direction as to what compounds form which prodrug form.

Thus, it can safely be concluded that the instant disclosure fails to provide an enabling disclosure for the pharmaceutically acceptable prodrugs of a compound of formula (I) or an agent for regulating stress.

4. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes mellitus, hyperlipidemia, obesity or anorexia, does not reasonably provide enablement for prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999, F.2d 1557, 1561 (Fe. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should

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proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75, F.3d 1558, 1564 (Fed. Cir. 1996).¹

The factors that may be considered in determining whether a disclosure would required undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) at 1404 where the court set forth the eight factors to consider when assessing if disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdsApls 1986) at 547 the court recited eight factors:

- 1) the nature of the invention;
- 2) the breadth of the claims;
- 3) the predictability or unpredictability of the art;
- 4) the amount of direction or guidance presented;
- 5) the presence or absence of working examples;
- 6) the quantity of experimentation necessary;
- 7) the state of the prior art; and,
- 8) the relative skill of those skilled in the art.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

“Prevention” is defined in Webster's New World Dictionary as “to keep from happening; make impossible by prior action.” See Webster's New World Dictionary, 3rd College Ed., Webster's New World Dictionary Publishing, page 1067 - 1068 (1988).

There is nothing of record to provide support that the claimed agent for preventing diabetes mellitus, hyperlipidemia, obesity or anorexia in a given patient. Applicant is advised that although claim language, such as “preventing” lack enablement under 35 U.S.C. § 112, first paragraph, phrases such as “reducing the incidence,” “reducing the

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frequency," or "reducing the likelihood," etc. are considered by the Office to be enabling, assuming of course that the specification in question has adequate written description and support for the asserted and claimed utility.

Applicant asserts in claim 4 an agent for preventing diabetes mellitus, hyperlipidemia, obesity or anorexia. To prevent, as defined by Merriam-Webster Dictionary is to keep from happening or existing, which implies taking advance measures against something possible or probable. Furthermore, the definition of "to prevent" and the "act of preventing" embraces the complete 100% inhibition. Thus, the burden of enablement in the assertion of this claim is much higher than would be the case of enabling the treatment of the condition and is not achieved. As for the instant application in relation to the prior art, neither the prior art or the instant application enable for the prevention of diabetes mellitus, hyperlipidemia, obesity or anorexia by a claimed agent. That being stated, nowhere in the instant application has the efficacy of the elected compound(s) been enabled to prevent the diabetes mellitus, hyperlipidemia, obesity or anorexia. Since absolute success is not reasonably possible with most diseases/conditions, the specification, which lacks an objective showing that of diabetes mellitus, hyperlipidemia, obesity or anorexia can actually be prevented, is viewed as lacking an adequate written description of the same.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

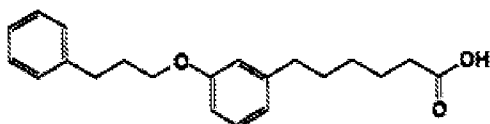
A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by **Tajima et al** (WO 99/11255 A1).

Tajima et al disclose the following compound [see page 131],



, which is capable of releasing a cation, and the compound or an agent is used for the treatment of metabolic disorders, such as diabetes, obesity disorders and hypertension. The above compound can be considered as an agent and property of regulating 14273 is inherently related the above disorders.

A kit or an agent is only limited to the preamble and not a required outcome of the method, MPEP 2111.02 reads, "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed inventions, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations. Then the preamble is not considered a limitation and is no significance construction." Therefore as long as a reference describes groups on the claimed compound and is in a format suitable for the intended use as claimed by applicant, the reference components are deemed to anticipate the claimed invention. Thus, the kit or an agent is anticipated by the groups taught by the compound taught by the **Tajima et al** and satisfies all required groups.

Therefore, the above compound anticipates instant claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

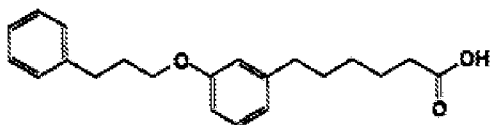
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-6, 10, 11, 15-18 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tajima et al** (WO 99/11255 A1) in view of **Gimeno et al** (WO 02/067868 A2) and **Shoda et al** (WO 2003/070686 A1).

Tajima et al teaches the following compound [see page 131],



, which is capable of releasing a cation, and the compound or an agent is used for the treatment of metabolic disorders, such as diabetes, obesity disorders and hypertension. **Tajima et al** also teach alkoxy groups

[see page 162-165], CF₃ [see page 184] chlorine [see page 185] on the aromatic moieties.

The differences between **Tajima et al** and instant claims are as follows:

(i) **Tajima et al** fails to teach an agent or a kit for regulating 14273 receptor function;

(ii) **Tajima et al** fails to teach specific groups at specific positions on the aromatic moieties.

With regard to (i) of above, **Gimeno et al** teach a method for identifying a compound capable of treating a metabolic disorder characterized by aberrant 14273 polypeptide activity, comprising assaying the ability of the compound to modulate 14273 polypeptide activity, thereby identifying a compound capable of treating a metabolic disorder characterized by aberrant 14273 polypeptide activity [see claim 24]. It is obvious for a person skilled in the art to measure the 14273 receptor function adjusting activity of the compound described by **Tajima et al** and to apply the compound to such diseases as diabetes, hyperlipidemia and obesity.

With regard to (ii) of above, **Tajima et al** fairly suggested alkoxy, chlorine and CF₃ groups on the aromatic moieties. Nevertheless, **Shoda et al** teach structurally similar compound. **Shoda et al** also teach fluorine substitutions at various positions of the aromatic moieties [see, for example CAS RN# 590412-64-9, 590412-62-7, 590412-60-5], and other halogens, such as bromine or chlorine [see, for example CAS RN# 590412-58-1, 590412-56-9].

In summary, **Tajima et al** teach applicants core structure and its use in the treatment of metabolic disorders, such as diabetes, obesity disorders and hypertension. **Gimeno et al** teach a method for identifying a compound capable of treating a metabolic disorder characterized by aberrant 14273 polypeptide activity, comprising assaying the ability of the compound to modulate 14273 polypeptide activity, thereby identifying a compound capable of treating a metabolic disorder characterized by aberrant 14273 polypeptide activity. **Shoda et al** teach structurally similar compounds with fluorine substitutions at various positions of the aromatic moieties, and other halogens, such as bromine or chlorine. Therefore, a skilled person in the art would immediately recognize the various substitutions, such as fluorine atoms, on the aromatic moieties, since these compounds expected to show different properties, which may be more effect over others in the treatment of metabolic disorders.

It would have been obvious to a person of ordinary skill in the art, at the time of invention was made, to have modified the references teachings, such as substituting aromatic moiety with fluorine atoms at various positions, and arrive at instant applicants' compound with a reasonable expectation of success. A skilled person in the art would be motivated to combine the teachings of the above cited prior art, because of their pharmaceutical importance in the treatment of metabolic disorders, also these kind of modifications are within the scope of skill person through a routine experimentation.

Conclusion

10. No Claim is allowed.

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhakar Katakam whose telephone number is 571-272-9929. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sudhakar Katakam/
Examiner, Art Unit 1621